From the
INTERNATIONAL SEARCHING AUTHORITY

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220 1134 WOOR001

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/051679	30.07.2004	31.07.2003

International Patent Classification (IPC) or both national classification and IPC
C07D221/12, C07D401/12, C07D407/12, A61K31/473

Applicant
ALTANA PHARMA AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/051679

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☐ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 10,11 (industrial applicability)

because:

☒ the said international application, or the said claims Nos. 10,11 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-11
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-11
Industrial applicability (IA)	Yes:	Claims	1-9
	No:	Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/EP2004/051679

Re Item III

Claims 10,11 relate to subject matter considered by this Authority to be covered by the provisions of Rule 67.1 (iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject matter of these claims, cf. Article 34(4)(a)(i) PCT.

Re Item V

1- Reference is made to the following documents cited in the search report:

d1: WO 97 28131 A
d2: WO 97 35854 A
d3: WO 99 05113 A
d4: WO 00 42018 A
d5: WO 00 42034 A
d6: WO 02 05616 A

2- Novelty
The present 6-phenylphenanthridine derivatives of formula (I) are novel vis-à-vis the 6-phenylphenanthridines of d1 to d6 on account of the substituent C(R7)=N-NCOR8 bound to the phenyl ring.
Accordingly, claims 1 to 11 do comply with the requirement of Art. 33.2 PCT since they all relate to the compounds of formula (I).

3- Inventive step
3.1-The applicant has set himself the task of providing novel phosphodiesterase (PDE) inhibitors, specifically PDE-4 inhibitors, which may be used in the treatment of a broad variety of conditions including airway obstructions, asthma, disorders of inflammatory nature and erectile disfunctions.
Documents d1 to d6 relate to 6-phenylphenanthridine derivatives having the same use of present compounds. Considering the chemical structures of the compounds disclosed in d1 to d6, it appears that any of these documents can be regarded as the closest prior art.
The results disclosed in Table A of the present application provide the evidence that substantially all the claimed compounds inhibit the PDE-4.
The objective technical problem may therefore be seen in the provision of further PDE4

inhibitors.

3.2- The solution to this problem is represented by present compounds of formula (I) which are 6-phenylphenanthridine derivatives characterised in that the phenyl is substituted by a hydrazide group.
From documents d1 to d6 it is evident that the PDE inhibiting activity is maintained over a broad variety of substitutions to the 6-phenyl group. Additionally, observing the experimental results disclosed in the Tables A of d1 to d6 (which refer to tests of activity carried out using the same methodology), it appears that not only the qualitative activity as PDE-4 inhibitors is maintained but also the quantitative activity, expressed in terms of - log IC50, is only slightly affected by the nature of the substituent of the phenyl ring. For instance, the compounds 1 and 13 of d1, 1, 5, 6, 7 of d2, have the same stereochemistry and the same substitution pattern on the phenanthridine ring and differ only on account of the substituents on the phenyl. Their quantitative activities are very similar in that they range from 6.44 to 7.73.
It appears that the skilled person, considering the disclosure of d1 to d6, would deduce that the PDE-inhibitory activity of the 6-phenylphenanthridines is substantially unaffected by the nature of the substituent on the phenyl ring. Accordingly, faced with the technical problem of providing further PDE inhibitors he would try to modify the substitution pattern of the phenyl ring by introducing any substituent.
Hence, it is considered that the provision of th eocmpounds of formula (I) does not involve any inventive activity.

4- The expression "predominantly fluorine-substituted" used in the claims is unclear (Art.6 PCT) in that it does not allow the exact determination of the degree of fluorination of the groups concerned.